|  |  |  |
| --- | --- | --- |
| **Gene** | **Functiona** | **Functional/Phenotypic variation in MSb** |
| CD40 | CD40 interacts with the CD40 ligand, located primarily on T cells, playing a role in T cell-dependent immunoglobulin class switching, memory B-cell development, and other processes. | CD40-bearing cells (mostly macrophages or microglial cells) can be found in perivascular infiltrates of brain active lesions. An increased expression of CD40L+ cells has also been observed in the brains of patients [1, 2]. |
| CD5 | CD5 is a scavenger-like receptor expressed in association with the antigen-specific receptors on T and B-1a lymphocytes. | CD5 expression on B lymphocytes is significantly higher in patients with active MS when compared to patients with clinically stable disease.  High levels of CD5+ B-cells independently associate with increased risk of early conversion to MS in clinically isolated syndrome (CIS) patients [3, 4]. |
| CD80 | CD80 (or B7-1) provides co-stimulatory, regulatory signals for T lymphocytes as a consequence of binding to the CD28 and CTLA4 ligands on T cells. | The CD80/CD86-CD28/CD152 costimulatory interactions involved in the initiation, reactivation, and progression of the immunopathology in MS. Increased expression of B7-1 can be detected in perivenular inflammatory cuffs of acute MS plaques [5, 6]. |
| CD86 | Similarly to CD80, CD86 (or B7-2) delivers a second signal to T cells by interaction with CD28 or CTLA4. | CD86 expression is higher on monocytes derived from secondary progressive MS patients compared to those from relapsing-remitting MS or from healthy controls. Part of the therapeutic mechanism of IFNbeta may be to down-regulate CD86 expression [7]. |
| CIITA | CIITA is a positive regulator of class II major histocompatibility complex gene transcription. | CIITA variation increases MS risk, and this appears to depend on the presence of HLA-DRB1\*1501 [8, 9]. |
| CXCR5 | CXCR5 is the receptor for the B-zone chemokine CXCL13 and it is involved in B-cell relocalization. | Increased CXCR5 levels can be found in primary progressive MS patients. Glatiramer acetate decreases the expression of this chemokine receptor [10, 11]. |
| FCRL3 | FCRL3 is a receptor for the Fc region (FcRs) of immunoglobulins. Such molecules modulate cellular and humoral immunity by linking their antibody ligands with effector cells of the immune system, and participate in autoimmune disorders. | Some variants of the Fc-receptor like-3 gene are involved in protection against MS, or in susceptibility to the disease [12, 13]. |
| GALC | GALC is a lysosomal enzyme involved in the catabolism of galactosylceramide, a major lipid in myelin, kidney and epithelial cells. | GALC substrates are major components of the myelin sheet [14]. |
| ICAM3 | ICAM 3 is an intercellular adhesion molecule and it is potentially the most important ligand for LFA1 in the initiation of the immune response. | ICAM3 expression is higher in cerebrospinal fluid and in brain lesions of MS patients [15, 16]. |
| IL12A  (p35) | Subunit in 2 distinct heterodimeric cytokines: interleukin-12 (IL12) and IL35. | Relapsing-remitting MS patients have increased expression of IL12A in whole blood [17]. |
| IL12B  (p40) | IL12B heterodimerizes with the IL12 p35 subunit (IL12A) to form IL12, and with the IL23 p19 subunit (IL23A) to form IL23. | IL12B polymorphisms are associated with MS. Serum levels are decreased during sustained treatment with IFN-beta1b [18, 19]. |
| IL12RB1 | IL12RB1 binds interleukin-12 with low affinity and is involved in IL12 transduction. When associated with IL12RB2 it forms a functional, high affinity receptor for IL12. It associates also with IL23R to form the interleukin-23 receptor. | The beta1 chain is part of the IL12 and IL23 receptor. IL23 may have a role in CNS inflammatory demyelination [20]. |
| IL6 | IL6 is a inducer of the acute phase response. It plays a role in the final differentiation of B-cells into Ig-secreting cells. Involved in lymphocyte and monocyte differentiation. | IL6 serum levels are higher in relapsing-remitting MS patients compared to controls. This molecule might reflect the global activity of the immune system in MS [21, 22]. |
| IL7R | IL7R is the receptor for interleukin-7, a glycoprotein involved in the regulation of lymphopoiesis. This ligand-receptor complex contributes to the normal development of T cells. | IL7R genotype influences susceptibility to MS. Increased soluble IL7Rα levels, as well as increased IL-7 levels, can be detected in patients with the predisposing IL7R variant [23, 24]. |
| MAPK1 | MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. | The MAPK signaling cascade is upregulated in stress, immune response and autoimmune demyelinating disorders [25]. |
| NFKB1 | NF-kappa-B is a transcription factor present in almost all cell types; it is the endpoint of a series of signal transduction events related to immunity, inflammation, cell growth, differentiation, tumorigenesis. | NFKB pathway is upregulated in MS. Animal models demonstrate positive effects of attenuating central NFKB activation [26]. |
| TNFRSF1A | TNFRSF1A is a receptor for TNFSF2/TNFα. It contributes to the induction of cytocidal and non-cytocidal TNF effects. | Some polymorphisms in the gene (i.e. the amino acid substitution R92Q) influence MS risk and may increase proinflammatory signals [27, 28]. |

**a.** Function drawn from [http://omim.org](http://omim.org/) or [http://www.uniprot.org](http://www.uniprot.org/).

**b.** Arbitrary selection of studies and/or reviews that are representative of the prevailing view of the pathogenetic role in MS

**Supplementary Table 6 References**

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